What is claimed:

1. A method for preparing an internucleotide phosphorothioate linkage enriched in the Sp enantiomer between a synthon having a hydroxyl moiety at the 5' position and a 2'-substituted nucleoside having an activated phosphate moiety at the 3'-position comprising selecting a coupling agent having a pKa ranging from about 3.3 to about 4.5 and coupling said synthon to said 2'-substituted nucleoside in the presence of said coupling agent.

2. The method of claim 1 wherein said first synthon is bound to a support.

3. The method of claim 1 wherein said coupling agent has a pKa ranging from about 3.4 to about 4.4.

4. The method of claim 1 wherein said coupling agent has a pKa ranging from about 3.5 to about 4.3.

5. The method of claim 1 wherein said coupling agent has a pKa ranging from about 3.6 to about 4.3.

6. The method of claim 1 wherein said coupling agent has a pKa ranging from about 3.7 to about 4.3.

7. The method of claim 1 wherein said coupling agent is 5-(ethylthio)-1*H*-tetrazole.

8. The method of claim 1 wherein said 2'-substituent is attached to the 2'-position through an oxygen atom.

9. The method of claim 8 wherein said 2'-substituent is O-alkyl, $O(CH_2)_nOCH_3$, or $O[(CH_2)_nO]_mCH_3$, wherein n and m are from about 1 to about 10.

10. The method of claim 1 wherein said 2'-substiuent is 2'-O-alkyl.

11. The method of claim 10 wherein said alkyl group is C_1 to C_{12} alkyl.

12. The method of claim 11 wherein said alkyl group is methyl.

13. The method of claim 9 wherein said wherein said 2'-substituent is $O(CH_2)_nOCH_3$ wherein n is from about 1 to about 3.

14. The method of claim 9 wherein said 2'-substituent is $O(CH_2)_2OCH_3$.

15. The method of claim 1 wherein said activated phosphate moiety comprises a *B*-cyanoethyl protecting group.

16. The method of claim 1 wherein said activated phosphate moiety comprises an acetoxy phenoxy ethyl group.

17. A method for preparing an internucleotide phosphorothioate linkage enriched in the Rp enantiomer between a synthon having a hydroxyl moiety at the 5' position and a 2'-substituted nucleoside having an activated phosphate moiety at the 3'-position comprising selecting a coupling agent having a pKa ranging from about 6.0 to about 7.5 and coupling said synthon to said 2'- substituted nucleoside in the presence of said coupling agent.

18. The method of claim 17 wherein said sython is bound to a support.

19. The method of claim 17 wherein said coupling agent has a pKa ranging from about 6.2 to about 7.3.

20. The method of claim 17 wherein said coupling agent has a pKa ranging from about 6.4 to about 7.1.

21. The method of claim 17 wherein said coupling agent has a pKa ranging from about 6.5 to about 7.0.

22. The method of claim 17 wherein said coupling agent has a pKa ranging from about 6.7 to about 6.9.

23. The method of claim 17 wherein said coupling agent is an imidazolium derivative.

24. The method of claim 23 wherein said coupling agent is an imidazolium salt.

25. The method of claim 23 wherein said coupling agent is imidazolium trifluoroacetate, imidazolium triflate, imidazolium perchlorate, imidazolium acetate, imidazolium tosylate or imidazolium nitrate.

26. The method of claim 17 wherein said 2'-substituent is attached to the 2'-position through an oxygen atom.

27. The method of claim 26 wherein said 2'-substiuent is 2'-O-alkyl.

28. The method of claim 27 herein said alkyl group is methyl.

29. The method of claim 26 wherein said wherein said 2'-substituent is $O(CH_2)_nOCH_3$ wherein n is from about 1 to about 3.

30. The method of claim 29 wherein said 2'-substituent is $O(CH_2)_2OCH_3$.

31. The method of claim 17 wherein said activated phosphate moiety comprises a *B*-cyanoethyl protecting group.

32. The method of claim 17 wherein said activated phosphate moiety comprises an acetoxy phenoxy ethyl group.

33. A method for preparing an oligonucleotide having at least one region of internucleotide linkages that is enhanced in the Sp enantiomer comprising:

providing a nucleotide having a hydroxyl moiety at the 5'-position or a growing oligonucleotide chain having a hydroxyl moiety at the 5'-position;

coupling said nucleotide or growing oligonucleotide chain to a 2'-substituted nucleoside having an activated phosphate moiety at the 3'-position in the presence of a coupling agent having a pKa ranging from about 3.3 to 4.5;

repeating said coupling step until the desired number of linkages is established.

34. The method of claim 33 wherein said oligonucleotide having at least one region of internucleotide linkages that is enhanced in the Sp enantiomer is further processed to include another region of internucleotide linkages that is enhanced in the Sp enantiomer.

35. The method of claim 34 wherein said oligonucleotide having at least one region of internucleotide linkages that is enhanced in the Sp enantiomer is further processed to include at least one region of internucleotide linkages that is enhanced in the Rp enantiomer.

36. The method of claim 35 wherein said oligonucleotide having at least one region of internucleotide linkages that is enhanced in the Sp enantiomer and at least one region that is enhanced in the Rp enantiomer is further processed to include another region of internucleotide linkages that is enhanced in the Sp enantiomer.

37. A method for preparing an oligonucleotide having at least one region of internucleotide linkgages that is enhanced in the Rp enantiomer comprising:

providing a nucleotide having a hydroxyl moiety at the 5'-position or a growing oligonucleotide chain having a hydroxyl moiety at the 5'-position;

coupling said nucleotide or growing oligonucleotide chain to a 2'-substituted nucleoside having an activated phosphate moiety at the 3'-position in the presence of a coupling agent having a pKa ranging from about 6.0 to 7.5;

repeating said coupling step until the desired number of linkages is established.

38. The method of claim 37 wherein said oligonucleotide having at least one region of internucleotide linkages that is enhanced in the Rp enantiomer is further processed to include another region of internucleotide linkages that is enhanced in the Rp enantiomer.

39. The method of claim 37 wherein said oligonucleotide having at least one region of internucleotide linkages that is enhanced in the Rp enantiomer is further processed to

include at least one region of internucleotide linkages that is enhanced in the Sp enantiomer.

40. The method of claim 39 wherein said oligonucleotide having at least one region of internucleotide linkages that is enhanced in the Rp enantiomer and one region of internucleotide linkages that is enhanced in the Sp enantiomer is further processed to include another region of internucleotide linkages that is enhanced in the Rp enantiomer.